release was 2.8 ± 0.4 and 1.1 ± 0.1 U/μg protein respectively ($p < 0.01$). The presence or absence of HOE642 in the R buffer did not affect the rate of hypercontracture induced by R after 40 min of MI (75.2 ± 2.9 and 62.2 ± 2% of hypercontracted cells in the control and HOE642 group respectively (p = NS)), nor did influence LDH release (p = NS). *Conclusion:* 1) Severe acidosis induced by ischemia is not a prerequiste for harmful Na^+/H^+ exchange during energy deprivation. 2) Inhibition of Na^+/H^+ exchange during energy deprivation, but not during reoxygenation, protects myocytes against reoxygenation injury.

784 Ischemic Mechanisms of Myocardial Dysfunction

Wednesday, March 27, 1996, 10:30 a.m.–Noon
Orange County Convention Center, Room 224F

10:30

784-1 Blocking the Endogenous Increase in Hsp 72 Increases Susceptibility to Hypoxia and Reoxygenation in Isolated Adult Feline Cardiocytes

Masayuki Nakano, Douglas L. Mann, Anne A. Knowlton. VA Medical Center, Houston, Tx; Baylor College of Medicine, Houston, Tx

Heat shock protein (HSP) 72 is a ubiquitous protein rapidly induced in response to ischemia, and thought to constitute an endogenous protective response. Previously, work has focused on the protective effects of *overexpression* of HSP 72. We wanted to test the hypothesis that prevention of the *normal physiological increase* in HSP 72 that occurs in response to stress would be deleterious; thus showing that the endogenous response in cardiac cells is an important line of defense against injury. Adult, feline cardiocytes were treated with a 14 mer phosphorothioate antisense (AS) to HSP 72, and exposed to mild (8 h) or severe (12 h) hypoxia. AS treatment converted mild injury to severe injury, as evidenced by an increase in LDH release, a decrease in MTT uptake, and a decrease in %live cells compared with control cells and cells treated with the complementary sense sequence. With severe hypoxia, there was less difference among groups, though indices of injury were worse for the AS treated cells. A 40% decrease in HSP 72 levels was seen in AS treated cells after hypoxia compared to control cells. A dose response study with 10 to 50 ug of antisense showed no further reduction of HSP 72. We conclude that: 1) Down-regulation of the endogenous, stress-induced increase in HSP 72 with AS increases the susceptibility of adult cardiac myocytes to hypoxic injury; 2) HSP 72 is an important part of the cardiac response to hypoxia and reoxygenation.

10:45

784-2 Does Ischemic Preconditioning Attenuate Myocardial Dysfunction During Hibernation and Reperfusion?

Ulrich Sunderdiek, Stefan Tuschen, Uwe Schwanke, Simone Schmitz-Spanke, Jochen D. Schipke. *Inst. of Experimental Surgery, Univ. of Düsseldorf, Germany*

The protective effect of ischemic preconditioning (IP) in reducing infarct size is well established, however, whether IP can attenuate myocardial dysfunction during coronary hypoperfusion (= hibernation) and reperfusion is unknown. Therefore, the effects of IP during 30 min of coronary hypoperfusion (HYP, CPP = 30 mmHg) and following reperfusion (Rep, CPP = 90 mmHg) were investigated on isolated, saline-perfused rabbit hearts. In two series (n = 8), with and without IP (3 min no-flow and 8 min reperfusion) LVPmax (mmHg), dP/dtmax and dP/dtmin (mmHg/s) and MVO2 (μl/100 g/beat) were assessed. *Results:* The effects of HYP were similar in both series, whereas in the IP-group, recovery during Rep was significantly improved.

	LVPmax	dP/dtmax	dP/dtmin	MVO2
Ctrl	101 ± 11	1420 ± 230	−1270 ± 150	32.2 ± 5.4
HYP	78 ± 9	980 ± 170	−930 ± 170	23.7 ± 5.4
Rep	80 ± 16	1070 ± 220	−960 ± 220	25.6 ± 6.6
Ctrl	121 ± 13	1990 ± 170	−1480 ± 130	58.6 ± 10.4
IP HYP	80 ± 11	1040 ± 120	−1030 ± 130	30.2 ± 4.6
Rep	111 ± 13*	1800 ± 210*	−1440 ± 110*	50.6 ± 6.1*

mean ± SEM; *$p < 0.05$ vs. HYP

To investigate the possible underlying mechanism of this protective effect during Rep, the A1-antagonist DPCPX (5 μM) was administered before the 3 min no-flow in a third series (n = 7). Recovery in this group was less pronounced compared to the IP-group (LVPmax reached 88% of control, dP/dtmax 74%, dP/dtmin 78% and MVO2 77%). *Conclusions:* IP provides a protective effect by attenuating ventricular dysfunction during reperfusion after coronary hypoperfusion. This protective effect, at least in part, is mediated via adenosine-A1-receptors.

11:00

784-3 Repetitive Exercise-Induced Ischemia in Patients With Stable Angina Causes Cumulative and Prolonged Left Ventricular Dysfunction Due to Myocardial Stunning

Christopher Rinaldi, André Linka, Navroz Masani, Roger Hall. *University Hospital of Wales, Cardiff, Wales, U.K.*

We have previously shown that myocardial stunning causes persistent left ventricular (LV) dysfunction after exercise-induced ischemia. To determine the effects of repeated exercise-induced ischemia on LV function we studied 12 patients (mean age 62 ± 5 years) with stable angina and angiographically-proven coronary disease. Each underwent 2 consecutive symptom-limited treadmill tests, one hour apart. Quantitative echocardiographic assessment of systolic and diastolic LV function (ECHO) was performed at baseline and at regular intervals after each exercise test. *Results:* Heart rate, blood pressure and ST changes returned to baseline within 10 mins of exercise in all cases. There were no differences between the 2 tests in exercise duration (328 ± 164 vs 334 ± 154 secs), maximum ST depression (2.1 ± 1 vs 1.9 ± 1.1 mm) or incidence of chest pain. ECHO data (mean ± s.d.) are as follows [SF = shortening fraction in the ischemic region (%), EF = ejection fraction (%), IRP = isovolumic relaxation period (ms)].

	Exercise test 1			Exercise test 2			
	pre	30' post	60' post	30' post	60' post	2 h post	4 h post
SF	3.3 ± 0.5	1.7 ± 0.9*	2.4 ± 0.7	1.3 ± 1.0†	–	2.4 ± 1.1*	3.4 ± 0.8
EF	56 ± 7	49 ± 12*	53 ± 9	45 ± 11*	–	51 ± 7	56 ± 8
IRP	100 ± 12	118 ± 13*	116 ± 9	125 ± 10†	123 ± 12†	118 ± 14*	100 ± 11

†$p < 0.01$ vs pre exercise; *$p < 0.05$ vs pre exercise

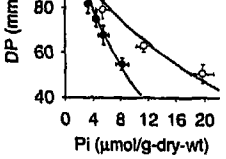
In concordance with previous observations, exercise-induced stunning was characterized by impaired regional and global contractile function and impaired (prolonged) early relaxation. These changes were more severe and prolonged after the second exercise test, despite similar indices of ischemia and exercise performance. We conclude that repeated exercise-induced ischemia causes cumulative LV dysfunction due to myocardial stunning.

11:15

784-4 Relative Contributions of Coronary Perfusion Pressure and Inorganic Phosphate in Mediating Contractile Dysfunction During Mild Coronary Flow Reductions

Masami Miyamae, S. Albert Camacho, William D. Rooney, Michael W. Weiner, Vincent M. Figueredo. *UCSF, San Francisco, CA*

Reduced coronary flow (↓CF) decreases contractility. Previous studies suggest that intracellular inorganic phosphate (Pi) (and not calcium, pH or ATP) is an important mediator of decreased contactility during mild ↓CF. However, the role of decreased coronary perfusion pressure (CPP) remains uncertain. To determine the relative contributions of CPP and Pi in mediating contractile dysfunction during ↓CF, the relationship between developed pressure (DP) and Pi was compared during ↓CF (decreased CPP) and hypoxia (CPP unchanged). Perfused rat hearts were subjected to: 1) mild graded ↓CF (100–50% CF, n = 12), or 2) graded hypoxia (100–40% O_2, n = 11) in the presence of iodoacetate (IAA) to attenuate changes in pH. 31P-NMR studies showed no decrease of pH or ATP during mild graded ↓CF or hypoxia. There was an inverse exponential relationship between DP and Pi during ↓CF and hypoxia (figure).



However, the exponential constant was ≈50% greater during ↓CF vs. hypoxia (0.09 for ↓CF; 0.04 for hypoxia). Since decreased CPP was the major difference between ↓CF and hypoxia protocols, these data suggest